Does Early Administration of Tranexamic Acid Reduce Blood Loss and Perioperative Transfusion Requirement in Low Energy Hip Fracture Patients?

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Background

Antifibrinolytic medications such as tranexamic acid (TXA) have been shown to reduce blood loss and transfusion requirement in trauma and surgical patients across numerous sub-specialties[1]. In trauma surgery, a large multi-center randomized controlled trial (CRASH-2) demonstrated reduced risk of death from bleeding and all-cause mortality with early, continuous use upon presentation to a trauma center[2, 3]. In orthopedic surgery, TXA is well studied for use in elective hip and knee replacement as well as spine surgery [4-6]. At Mayo Clinic Rochester, the routine administration of tranexamic acid has become part of the typical protocol for elective hip and knee replacement as well as major spinal procedures. The use of TXA in orthopedic trauma patients is an area of current research interest. A 2010 prospective randomized, controlled trial of perioperative TXA demonstrated reduction in transfusion requirements for intertrochanteric hip fractures treated with short, cephalomedullary nails. This was clinically, though not statistically, significant [7]. We recently conducted a randomized, controlled trial at this institution to evaluated the use of TXA in patients with femoral neck fractures treated with hemiarthroplasty or total hip arthroplasty and found clinically, albeit not statistically, significant reduction in transfusion requirement[8]. Perhaps tempering the effect seen with perioperative administration of TXA is the blood loss that occurs prior to surgery, the so-called “hidden” blood loss that can be as substantial as 1/3 of total blood loss from a

hip fracture [7, 9]. This raises the question whether administration of tranexamic acid at the time of initial presentation after fracture could improve the perioperative care of these patients by decreasing the proportion of patients requiring transfusion and decreasing total blood loss. This would have potential implications for infection, morbidity and all-cause mortality from such fractures.

Recent literature has substantiated the safety of TXA administration in this fragile hip fracture patient population. A prospective, randomized trial assessing perioperative TXA administration for extrcapsular hip fractures treated with cephalomedullary nails published in 2018 demonstrated reduction in blood loss and 20% reduction in transfusion rate without any increase in thrombotic complications[10]. Additionally, the protocol for bolus and subsequent infusion dosing of TXA initially recommended in the CRASH-2 trial has been validated with a recently published literature review evaluating the use of TXA in the pre-hospital setting to limit hemorrhage. They determined that the risk for vascular events was not increased due to drug administration above and beyond the anticipated increased risk due to the insult of trauma and hypovolemia secondary to blood loss. They concluded that this medication and dosing was safe for use even outside of the hospital setting[11].

Methods

A single-center, prospective randomized study is proposed. Consecutive patients presenting with intertrochanteric hip fractures will be treated with tranexamic acid. Treatment will be initiated in the emergency department according to a previously studied protocol for trauma patients.

Inclusion criteria

-AO/OTA fracture classification 31A
-Surgically treated with sliding hip screw or cephalomedullary nail (short or long)
-Low energy, isolated injury

-Age greater than 18 years old

Exclusion Criteria

-Intracapsular hip fractures: AO/OTA fracture classification 31B-C

-Polytrauma patients

-Creatinine clearance less than 30 mL/min

-History of unprovoked VTE and/or recurrent VTE

-Known history of Factor V Leiden, protein C/S deficiency, prothrombin gene mutation, anti-thrombin deficiency, anti-phospholipid antibody syndrome, lupus anticoagulant

-Pregnancy or breastfeeding (pregnancy tests will be performed on all patients of child-bearing potential)

-History of CVA, MI, or VTE within the previous 30 days

-Coronary stent placement within the previous 6 months

-Disseminated intravascular coagulation

-Intracranial hemorrhage

Initial Patient Encounter

The Orthopedic Trauma Service (OTS) in the emergency department will perform a history and physical exam. Hip radiographs will be obtained to evaluate fracture type and indicated operative procedure. If study criteria are met, informed consent will be obtained either from the patient or legally authorized representative. After consent is obtained, treatment will be initiated in the emergency room with study medication obtained by ED pharmacy.

TXA will be administered intravenously via bolus dose of 1g over ten minutes and an additional 1g over the subsequent 8 hours, in accordance with a previously studied protocol utilized in the CRASH-2 trial [2, 3]. Patients in the control group will receive a placebo medication in the ED. Neither group will receive perioperative bolus dosing of TXA.

Operative Course

Prior to surgery, patients will undergo pre-anesthesia medical clearance and stabilization in coordination with the hospitalist medicine team. Anesthetic type (regional vs. general) will be at the discretion of our anesthesia colleagues.

During surgery, crystalloid maintenance fluids will be administered at a rate of 1.5 cc/kg/hour. Blood losses will be replaced with crystalloid solution in a 3:1 ratio, 5% albumin in a 1:1 ratio, or a combination. Changes of 20% in baseline heart rate or blood pressure which are felt to be due to hypovolemia will be managed with boluses of 10 cc/kg crystalloid solution or 500 cc of 5% albumin. Intraoperative transfusions will be given for hemoglobin levels less than 8 g/dL. If transfused, one unit of packed red blood cells will be administered at a time, with reassessment after each unit. Transfusion triggers will not apply to patients with active myocardial ischemia or hemorrhagic shock.

Surgical management will include either sliding hip screw or cephalomedullary nailing as clinically indicated, performed in routine fashion. Hemostasis will be attained prior to wound closure.

Hospital Course

While admitted to the hospital, all patients will be co-managed between the orthopedic trauma service and the hospitalist medicine service. Hemoglobin levels will be checked daily through postoperative day three, and as indicated thereafter. Conservative triggers for blood transfusion will be used for all patients. Transfusion will be considered for all patients with hemoglobin values of less than 8 g/dL with persistent symptoms or history of significant cardiac disease that may render the patient less able to compensate for significant anemia. Blood transfusion will be considered in all patients with hemoglobin less than 7 g/dL, regardless of symptoms. Hemoglobin triggers will not apply to patients with active myocardial ischemia or hemorrhage. When the decision is made to transfuse, one unit of packed red blood cells will be administered at a time, with reassessment after each unit.

All patients will receive standardized DVT prophylaxis including lower extremity sequential compression devices and low-molecular weight heparin, unless medically contraindicated or full therapeutic anticoagulation is required. Postoperative mobilization will begin as soon as clinically indicated.

Each hospital day, patients will be clinically evaluated for signs of symptomatic venous thromboembolic event (VTE), myocardial infarction (MI), cerebrovascular accident (CVA), and wound complications. Diagnostic workup will be performed only in the setting of acute symptoms. There will be no routine or mandatory screening with the exception of daily clinical evaluation by a member of the OTS trauma team as well as the hospitalist medicine team. VTE will be defined as symptomatic deep venous thrombosis diagnosed by duplex ultrasound, or pulmonary embolism diagnosed by contrast spiral chest CT or ventilation-perfusion scan. MI will be diagnosed using electrocardiogram and serial serum cardiac enzymes. CVA will be defined as transient ischemic attack or stroke diagnosed by head CT or MRI. Wound complications will include hematoma formation, dehiscence, and deep or superficial infection.

Clinical Follow-up

Patient follow-up and disposition will be at the discretion of the treating surgeon. For the purposes of this study, patients will be followed for a period of six months from the day of surgery. At the time of follow-up, patients will be assessed for the incidence of complication including VTE, MI, CVA, wound complication, and all-cause mortality. If patients are not able to return to clinic, they (or their legally authorized representative) will be contacted by phone.

Primary Outcome

-Proportion of patients transfused at least 1 unit of packed red blood cells during hospital admission

Secondary Outcomes

-Mean number of units transfused per patient

-Calculated blood loss

-Incidence of symptomatic VTE diagnosed within 6 months of surgery

-Wound complications diagnosed within 6 months of surgery

-MI diagnosed within 6 months of surgery

-CVA diagnosed within 6 months of surgery

-All-cause mortality at 6 months

Safety Monitoring

All patients will be monitored for signs and symptoms of reaction to the administration of tranexamic acid during administration and throughout their hospital stay. Their care will otherwise be performed in standard fashion, coordinated between the orthopedic trauma service and the hospitalist medicine team. A Data and Safety Monitoring Board (DSMB) comprised of three outside faculty members ([redacted]) will meet quarterly. Outcome data including adverse events (VTE, MI, CVA, mortality, wound complications) will be compiled quarterly and reviewed by the DSMB. In order to facilitate evaluation of complications for potential relatability, patients may be selectively unblinded at the request of the DSMB. They will then determine if the complication is likely or unlikely to be related to the study intervention. If there is concern for increased complication rates, the data will be submitted to the Department of Biostatistics for evaluation and comparison to a previously studied control group. In the event of increased adverse events in the treatment group, data would be submitted to the appropriate governing body for review.

Statistical Considerations

Randomization and Blinding

Subjects will be randomized into one of two study groups: TXA administration (treatment) or placebo (control). Subjects will be assigned to either the treatment group or control group using a pre-generated blocked randomization design. The randomization schedule will be developed by the study statistician and will be provided to Research pharmacy personnel who will make the study group assignment. Medications

will then be delivered to the emergency department in packaging that does not delineate whether it contains placebo or tranexamic acid. Thus, the patient, treating surgeon, emergency department physician, residents, hospitalist group, anesthesiologist, and data collectors will remain blinded to the treatment assignment.

Analysis

The primary outcome will be the proportion of patients transfused at least 1 unit of packed red blood cells during hospital admission. Secondary outcomes will include mean number of units transfused per patient, calculated blood loss, and incidence of adverse events at six months including: VTE, MI, CVA, wound complications, and all-cause mortality as previously defined. The cohort of patients treated with early administration of TXA in the ED will be compared to a control group who were not treated with TXA at any point. All outcomes will be reported descriptively using appropriate summary statistics, including 95% confidence intervals, where appropriate. Baseline variables, including fracture type, surgical procedure, presenting hemoglobin, history of coronary artery disease, American Society of Anesthesiologists (ASA) score, length of surgery, length of anesthesia and type of anesthesia will be summarized overall and separately by study group; because this is a prospective, randomized trial, no formal between-group comparisons of baseline covariates will be performed. Adverse events as well as the primary and secondary outcomes occurring during the hospital stay and up to six months following surgery will be evaluated using chi-square tests and logistic regression (for categorical variables) if complete follow-up is obtained for the study subjects If follow-up varies because of subject withdrawal or lack of response at 6 months, these outcomes will be estimated and evaluated using survivorship methods such as Kaplan-Meier estimation and Cox proportional hazards regression. Two-sample t-tests will be used to compare continuous variables between the study groups. All statistical tests will be two-sided and the threshold of statistical significance will be set at $\alpha = 0.05$.

Sample Size

In a prospective randomized, controlled trial conducted in Denmark evaluating a similar outcome in the same patient population, there was a transfusion rate of 84.6% in the control group, who never received

TXA [9]. However, a retrospective evaluation of the transfusion rate for the population of interest at our institution in 2014 with standard transfusion thresholds as reflected in the above described protocol was 50%. Utilizing this transfusion rate, the sample size was calculated to be able to detect a difference of 50% versus 25% (a reduction of risk by 1/2) between the control group and treatment group, respectively. A sample of 58 subjects per study group (116 in total) will provide 80% power to detect a difference in the proportion of patients receiving blood transfusion of 50% versus 25% (α=0.05, two-sided test) [10]. We will assume an attrition rate of at least 15%, thus the target sample size will be 78 patients per group, 156 in total.

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